REMARKS

The Office Action of April 20, 2005 has been reviewed and the remarks made have been carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for her thorough and detailed arguments. Claims 21-25, 27-30 and 43 are currently pending. Claim 25 is amended herein. Claims 37-42 are canceled herein without prejudice. No claims have been added herein.

REQUEST FOR CONTINUING EXAMINATION

This response to the Examiners Office Action is provided in light of the filing of a Request for Continued Examination under 37 CFR § 1.114 & 37 CFR 1.17(e). As such the finality of the previous rejection has been removed.

ACCEPTANCE OF DRAWINGS

Applicants gratefully acknowledge and thank the Examiner for her acceptance of the drawings filed for this case pursuant to 37 CFR § 1.121(d).

35 USC § 112, FIRST PARAGRAPH - NEW MATTER REJECTION

The Examiner rejected pending claim 25 under 35 USC § 112, first paragraph as being indefinite for inappropriately reciting "a second non-human transgenic mammal" where no "first" such animal was recited. This concern has been addressed through amendment to claim 25 and is now overcome. Reconsideration is requested.

The Examiner rejected pending claims 37-42 under 35 USC § 112, first paragraph as being indefinite for reciting limitations not within the specification. This concern has been addressed and rendered moot through cancellation of the claims 37-42. These limitations can be addressed through a divisional filing as needed to protect Applicant's rights. Reconsideration is requested.

THE REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH – IMPROPER DEPENDENCY

Claim 25

Claim 25 was rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The objection has been addressed through a specific amendment to the claim to clarify, particularly point out, and distinctly claim the subject matter of the invention. Respectfully, this rejection is traversed. The pending claim is now believed to comply with the provisions of 35 U.S.C. § 112, second paragraph. Thus, the Examiner's rejection of claim 25 based on §112, second paragraph for inappropriate dependency is believed to be traversed. Reconsideration is respectfully requested.

THE REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner rejects claims 21-25, 37-30 and 43 under 35 USC § 112, first paragraph as failing to comply with the written description requirement. Respectfully, Applicant requests that any requirement for canceling the added material specified by the Examiner as "new matter" be withdrawn for the reasons set forth above. As for failing to meet the written description requirement the Applicant provides the following remarks and arguments. Reconsideration is respectfully requested.

Functional Fragment

Claims 21-25, 27-30 and 37-43 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not sufficiently described in the specification so as to comply with the Written Description requirement.

As previously presented, the Examiner continues to reject the use of the language "functional fragment thereof" in reference to specific proteins such as the cellulose binding domain, protein L, and various antibodies as unsupported by the specification. Generally, therefore, the Examiner is effectively stating that while the sequences of specific proteins may be known, and that their respective pharmacological or chemical activities may be known, the

knowledge of how to retain this chemical/biological activity in what is essentially a fusion protein with less than a whole protein sequence was not known by the prior art. With this the Applicants continue to fundamentally and vehemently disagree. For clarification of function Applicants have amended the independent base claims or the important dependent claims of note to recite "chemically functional fragment." More specifically, the Applicants also point out that the functional aspect of the proteins of note is their use as tools for purification. That is, the only physiological trait that they needed to retain was their ability to recognize certain bindable epitopes and be useful in known laboratory protocols or processes for purification purposes. This implicit limitation also limits the claims and limits the language "chemically functional fragment" thereof.

The role of the written description requirement under 35 U.S.C. § 112 has been the subject of much debate. However, the written description requirement had a shaky start in the Federal Circuit, but the court finally laid the controversy to rest in Vas-Cath, Inc. v. Mahurkar, when it affirmatively stated that written description and enablement are, in fact, separate and distinct requirements. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1560 (Fed. Cir. 1991). The court clarified that while the enablement requirement teaches how to make and use an invention without undue experimentation, the written description requirement serves "to put the public in possession of what the party claims" as its invention.

Relative to the instant rejections then, the specification and the teachings it represents must then clearly demonstrate that the applicant was in possession of the invention at the time the patent application was filed. Applicant maintains that this is and was adequately done.

Also, unlike the enablement requirement, adequate written description is a question of fact, not a question of scientific experimentation and the Wands factors as for enablement. Thus, under § 112 the applicant must essentially teach all subject matter claimed, as well as describe some aspect of the disclosed information with sufficient particularity such that it will act to preserve the right to later claim some or all of the information. Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986). Therefore, in the biological arts, if a claimed invention is insufficiently described in the original application, then it will be deemed "new matter," and will not receive the benefit of the initial filing date. 3 Donald S. Chisum, CHISUM ON PATENTS § 7.04 (Supp. 1997); 1 Irving Kayton, PATENT PRACTICE § 2.6 (Patent

Resource Inst., Inc. 6th ed. 1995). Moreover, the courts have consistently emphasized the fact-sensitive nature of the written description requirement.

Even given the above requirements, binding legal precedent and existing Patent Rules *do not* dictate that every specification must regurgitate every known and relevant scientific fact or discovery up to and including the instant invention to meet the written description requirement. To do so would be to make the act of adequately preparing a patent application a Herculean task and applications too long to be effectively processed.

First, Applicants point to the prior art and point out that in making the determination as to whether the written disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, and U.S. patents contemporaneous with the filing of this patent. That is to say they are presumed to know and utilize the basic tools of their trade and be conversant with the basic scientific techniques that make the instant application possible. In this way, practitioners in a field have a "common" language and a common set of protocols and techniques that are known. This is the basic level of understanding that qualifies a worker in the field. In the biotechnology realm this would include knowledge of the coding sequences of DNA, RNA as well as basic protocols such as the polymerase chain reaction and what constitutes a "Western Blot" or a "Northern Blot" laboratory protocol. In the same way, the instant claims recite a protein that retains its physiological function likely by retaining a key amino acid sequence responsible for a specific chemical or enzymatic effect. This then is the foundation for the use and recitation of a "functional fragment thereof" for a given protein species or hybrid.

Applicant also points out that the knowledge of the functional aspects of fusion proteins was well known in the contemporaneous art and that it can be used to inform the instant claims. Examples of relevant contemporaneous art include:

> **Factor X fusion proteins: improved production and use in the release in vitro of biologically active hirudin from an inactive alpha-factor-hirudin fusion protein.**
> Guarna MM, *et al.*, Protein Expr Purif. 2000 Nov;20(2):133-41.
>
> **Expression, immobilization, and enzymatic characterization of cellulose-binding domain-organophosphorus hydrolase fusion enzymes.**
> Richins RD, *et al.*, Biotechnol Bioeng. 2000 Sep 20;69(6):591-6.

Expression, purification and applications of staphylococcal protein A fused to cellulose-binding domain.
Shpigel E, *et al.*, Biotechnol Appl Biochem. 2000 Jun;31 (Pt 3):197-203.

Second, with regard to the nature of the specification in the instant matter, the uses therein disclosed need not be apparent to everyone; all that is required is that enablement, and the potential usefulness of the discovery is communicated to the skilled artisans of the relevant technology. Given the above citations, available to all workers in the field, the Applicants maintain that any needed teachings were sufficiently performed in the specification. This along with the Federal Circuit's repeated assertions that in the field of biotechnology the level of skill in the art is necessarily a high one, indicates that the written description requirements for the instant claims be determined not by the public at large but by scientists already trained in many of the basics of the technology and well-versed in standard protocols. Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co., 228 F.3d 1338, 1340 (Fed. Cir. 2000)("Patents, however, are written to enable those skilled in the art to practice the invention, not the public"); Enzo Biochem v. Calgene, Inc., 188 F.3d 1362 (Fed. Cir.1999); *and see*, Enzo Biochem v. Gen-Probe, Inc., 296 F.3d 1316, 1324, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002). Therefore, the Examiner's rejection of the claims 9, 10, 21, 22, 27 and 28 under 35 U.S.C. § 112, first paragraph, is overcome and reconsideration is requested. Webster Loom Co. v. Higgins, 105 U.S. 580, 26 L.eD. 1177, 1179 (1882).

Third, it should be pointed out that once a patent expires or a publication is made without a proprietary application being made the teachings are "dedicated" or provided to the public domain for public use. This includes the use of a prospective patentee as a reference point for the extent of the prior art and a reservoir of information that informs the claims and specification as filed.

Fourth, it should also be pointed out that it is well settled law that there is no longer a "flash of genius" requirement for patentability. That is, patentability does not rest on the development of new technology that completely eliminates prior art problems and difficulties; rather, patents can and should be issued to stepwise improvements in technology that are novel and otherwise meet the standards of the Patent Code. Cuno Eng'g Corp. v. Automatic Devices Corp., 314 U.S. 84, at 91 (1941) (proclaiming the "flash of genius" standard later abolished by institution of the current United States Patent Code of 1952); Graham v. John Deere Co., 383

U.S. 1, at 15-16 (1966) (Specifically overruling Cuno) (as applied here, the complete inhibition of the myriad difficulties associated with the production of a chemically active fusion protein/target polypeptide in a transgenic mammal production platform contemplating a purification methodology).

Finally fifth, the Examiner is also reminded that the Inventor is allowed "to be his own lexicographer," and that if this verbal license leads to any ambiguity the claims are to be construed "in connection with the other parts of the...patent application." Autogiro Co. of America v. United States, 384 F.2d 391 (Ct. Cl. 1967). Within the meaning of the patent application and the pre-existing contemporaneous prior art "functional fragment" is known as is "chemically functional fragment" to have a specific meaning regarding the physiological characteristics of a given sequence of protein. Respectfully, reconsideration is requested.

CBD

Applicants, note that these claims recite the binding regions of polypeptides derived from protein L, or the cellulose binding domain (CBD) or chemically functional fragments thereof. These proteins were known by artisans in the field at the time of filing and their pharmacological, chemical, and/or molecular activities were also known.

Moreover, regarding the rejected claims, the Examiner previously rejected claims 27-30 asserting that the term 'a fragment thereof' renders the claims indefinite because it is unclear which part or size fragment of protein L or cellulose binding domain is referred to. Respectfully, the claims have been amended to recite a "chemically functional fragment thereof." By requiring that the fragment be functional, it is clear that only those fragments capable of binding are covered. Specifically, the claims refer to fragments of protein L that are capable of binding the bindable epitope of the target polypeptide and fragments of cellulose binding domain that are capable of binding a matrix. That is, the chemical function. Therefore, Applicants respectfully request that this rejection be withdrawn. Moreover, these claims are supported by the Specification as filed. Please see the Summary of the Invention pages 1-2.

If Applicant's response is inapposite or if Applicant's assumptions are incorrect or inappropriate please inform the Applicant. Respectfully, Applicant therefore requests clarification and/or favorable reconsideration of the claims rejected hereunder.

The Rejection Under 35 U.S.C. §103(a)

Cheng et al., Schwarz et al., Radford et al., Wagner et al., Meade et al., and Nujiens et al.,

Claims 21-25, 27-30 and 43 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the Cheng *et al.*, reference in view of Schwarz *et al.*, Radford *et al.*, Wagner *et al.*, Meade *et al.*, and Nujiens *et al.* The rejection of the claims, as amended, is respectfully traversed.

As previously delineated the basic considerations which apply to obviousness rejections under MPEP § 2141 remain as follows:

(1) the claimed invention must be considered as a whole;

(2) the references must be considered as a whole and must knowingly suggest the desirability and thus the obviousness of making the combination;

(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(4) the reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Rijckaert, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). As pointed out below, the prior art not only fails to provide the suggestion, or incentive to combine, but also fails to provide any reasonable expectation of success for the piecemeal combination of the prior art into something resembling the instant invention.

Cheng et al.,

The Cheng *et al.*, patent teaches purifying a polypeptide from a mixture using an antibody. Respectfully, Cheng does not provide for altering the sequence of transgenically

produced molecule, does not discuss fusion proteins, does not discuss multivalent binding moieties, and does not discuss any modifications to the structure or amino acid sequence of an antibody or other polypeptide. This lack of guidance, lack of anything resembling "teaching" the invention is clear. Given this, and the controlling precedent cited above not only fails to render obvious the invention it also fails to make itself available for combination as anything resembling analogous art.

Moreover, Cheng *et al.*, fails to provide or teach the following:

a) milk or similar bodily derived substance;

b) purification of a transgenically derived molecule using a second transgenically derived molecule; or

c) modifying a polypeptide sequence to make purification easier through the use of known binding domains.

Respectfully, these deficiencies are not remedied by the piecemeal application of the other citations provided by the Examiner. That is, though the Cheng *et al.*, reference and other citations are tasked to providing a solution to the same or similar problem the solutions each provides is significantly different and either simply would not be combined by an artisan in one field (purification/ chromatography/ solution procession) with the art of another field (transgenic molecular biology/ genetic engineering) such that they are not analogous art available for combination or alternatively offer so many other possibilities toward some purification scheme as to lack and direct or purposeful teaching that could usefully be combined.

Schwarz et al,

Schwarz *et al.*, does not provide what Cheng *et al.*, lacks. Schwarz presents the use or bacteria derived protein L and its use in purification schemes. More specifically, Schwarz *et al.*, presents the use of protein L in the purification schemes for antibodies. It does not teach anything resembling the construction and purposeful manipulation of transgenic mammals or the directed alteration of target polypeptides for later biologic production and final production in milk or a biologically derived liquid feedstream. Likewise, it fails to mention, suggest or teach milk as a reaction mixture. For these reasons it too essentially functions as non-analogous art and

is unavailable for any combination. Moreover, the patent suggests that the methods provided therein are necessary and sufficient for the purification methods provided. That is, no other teachings are suggested. Respectfully, therefore, it is clear that this citation simply does not provide any suggestion for combination or alternate modes of purification that would make it available to combine with other prior art. Nor can it teach (due to its remoteness in time) any combination with Cheng *et al.*,.

Thus, neither of the amended independent claims 5 and 12 can be obvious over Schwarz *et al.*, either alone or in combination with Cheng *et al.*, given these remarks and those already provided, nor can any claims dependent upon them.

Radford et al.

Radford *et al.* also fails to provide what the Cheng *et al.*, and Schwarz *et al.* references lack. In fact Radford *et al.*, essentially only provides a citation discussing the cellulose binding domain (CBD) and the possibility of adding this domain to a polypeptide of interest. In this sense it catalogs what is known in the prior art about the CBD and offers its use for purification schemes -but offers little else. It does not suggest a multivalent polypeptide, transgenic mammalian production, or elution of these molecules from a biologically derived feedstream. Therefore, Radford offers little to the combination of Cheng *et al.*, and Schwarz – even if it could be combined with them.

Similar arguments and recitations can be made with each of the Wagner, Meade, and Nuijens citations. Each in turn fails to suggest a combination or is simply non-analogous art. With the unavailability of Cheng, Schwartz and Radford for combination as non-analogous art or simply through lack of any teaching to combine the other citations cannot maintain anything resembling an obviousness rejection.

The present invention, as recited in the amended independent claims offers the benefits of a novel structural method, transgenic production and a different method of polypeptide purification. If the invention as recited were obvious, then those skilled in the art would have long since adopted this invention. However, according to the art of record, those skilled in the art have <u>not</u> adopted the present invention, and therefore do not get the benefit of the invention. Therefore, it is proposed that independent claims 21, 25, and 27 and those claims dependent upon them, cannot be obvious.

Dependent claims 22-24, 28-30 and 43 being dependent upon and further limiting independent amended claims 21, 25 and 27 should also be allowable for that reason, as well as for the additional recitations they contain. Applicants respectfully request reconsideration of the rejection of the pending claims under 35 U.S.C. § 103(a) in view of the above amendments and remarks.

The Commissioner is authorized to charge any fee which may now or hereafter be due for this Repy/Amendment to GTC Biotherapeutics' Deposit Account No. 502092.

It remains Applicant's firm belief that the claims as provided are fully supported by specification generally with substantial literal support to its plain meaning at specific locations within the four corners of the specification. In addition, the Examiner is also respectfully reminded that the Applicants are allowed "to be..[their][sic] own lexicographer," and that if this verbal license leads to any ambiguity the claims are to be construed "in connection with the other parts of the...patent application." Autogiro Co. of America v. United States, 384 F.2d 391 (Ct. Cl. 1967). Respectfully, should the Examiner maintain her rejections, Applicants retain their right to appeal or petition this decision to the Board of Patent Appeals and Interference's. Reconsideration and withdrawal of these rejections is respectfully requested. Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 10/19/05

By: _____

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